UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,120	06/14/2001	David Thomas Dudley	5968-01-SMH	5646

7590 03/20/2003

SUZANNE M. HARVEY
WARNER-LAMBERT CO.
2800 PLYMOUTH ROAD
ANN ARBOR, MI 48105

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	10

DATE MAILED: 03/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

10

Office Action Summary	Application No.	Applicant(s)	
	09/868,120	DUDLEY ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendments filed December 18, 2002 have been entered.

The addition of claims 17-19 in amendments filed December 18, 2002

The outstanding objection is withdrawn in view of the amendments filed December 18, 2002.

The outstanding rejection of claim 14 under 35 USC 112, second paragraph is withdrawn in view of the amendments filed December 18, 2002.

Please note that the limitation "preventing arthritis" recited in claims 1 and 17 is not enabled by the specification. It is known in the art that there are so many types of arthritis and each type of arthritis may be caused by different etiologies and have different pathophysiologies. The claims are so broad that it encompasses all kinds of arthritis. Moreover, the specification does not set forth any working examples and guidance to one of skilled artisan to prevent arthritis in patients when they do not have the disease. It is highly unlikely and unpredictable to prevent every types of arthritis. Undue experimentation will be required to: 1) identify the patient population that would be suffered from the disease ahead of time and 2) prevent the disease to be manifested in the same patient population. Prevention of such disorders is not enabled by the instant specification. Examiner will favorably consider the expression such as "reducing the risk of".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Mynott et al. (WO 96/00082 provided in the International Search Report).

Mynott et al. teaches bromelain, a MEK inhibitor, is useful in a method of treating rheumatoid arthritis (See page 7, line 17- page 8, line 25; also, page 11, line 21-27; and claims 14-15).

Response to argument with regard to rejection under 35 USC 102(b)

Applicant's rebuttal arguments averring Mynott's failure to teach bromelain as MEK inhibitor have been considered, but are not found persuasive.

Mynott clearly teaches that bromelain is an agent that can block tyrosine phosphrylation including MAP kinase (also referred as MEK in the instant application, See page 1, line 5 in the Field of the Invention Section) (See Mynott, page 11, line 21- page 12, line 2, particularly page 11, line 24 - 30). Mynott further recites that bromelain is useful as treatment for rheumatoid arthritis (See particularly claim 14). In view of such teaching, the claims are properly rejected under 35 USC 102(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazawa et al. (The Journal of Biological Chemistry, 1998; 273(38): 24832-24838 from the International Search Report), Jackson et al. (The Journal of Pharmacology and Experimental Therapeutics, 1998; 284(2): 687-692 from the International Search Report), Henry et al. (Bioorganic & Medicinal Chemistry Letters, 1998; 8(23): 3335-3340 from the International Search Report), and McGilvray et al. (The Journal of Biological Chemistry, 1997; 272(15): 10287-10294) in view of Bridges (WO 98/37881 from the International Search Report).

Miyazawa et al. teaches that MEK is critically involved in interleukin-6 synthesis by Human fibroblast-like synoviocytes (FLSs), which exhibit inflammatory cells characteristic (See page 24832, col. 1, the abstract and the first paragraph). Miyazawa et al. also teaches that MEK inhibitor can block the activation of MEK and suppression the interleukin-6 production and TNF-α (See page 24837, col. 1, first paragraph and col. 2, second paragraph). Miyazawa et al. also teaches antagonizing interleukin-6 and TNF

would be effective in treating rheumatoid arthritis (See particularly page 24837, col. 1, second paragraph). Miyazawa et al also suggests that the inhibitors of MEK would be beneficial as rheumatoid therapy (See particularly page 24837, col. 2, last paragraph).

Jackson et al. teaches inhibition of MEK by a specific MEK inhibitor, SB220025, reducing both interleukin-1β and TNF expression and SB220025 being useful in method of treating chronic inflammation (See the abstract, also page 687; both columns; also page 690, col. 2, second paragraph; particularly page 691, col. 2, last paragraph).

Henry et al. teaches that pro-inflammatory cytokines such as TNF-α and interleukin-1-β play important role in inflammatory diseases such as rheumatoid arthritis (See particularly page 3335, first paragraph). Henry et al. also teaches that inhibition of MEK can inhibit TNF-α release and thereby beneficial to rheumatoid arthritis treatment (See page 3335, first paragraph and page 3339, last paragraph).

McGilvray et al. teaches the involvement of MAP kinase (MEK) pathway in the activation of monocytic cells during transmigration to inflammatory sites (See the abstract). McGilvray et al. teaches the selective inhibition of MAP kinase by MEK-1 inhibitor, PD98059, being useful for blocking and interrupting the adhesion and recruitments of human monocytes and thereby modulating the inflammatory response (See the abstract and page 10287, col. 2, second paragraph).

The primary references do not expressly teach the active compounds herein to be MEK inhibitors useful for the treatment of arthritis.

Bridges teaches that the active compounds herein are MEK inhibitors (See page 3, line 16 – page 22, line 29). Bridges also teaches the specific MEK inhibitor recited in claim 17 herein as a preferred MEK inhibitor (See page 22, line 24-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the MEK inhibitors of Bridges to treat arthritis such as osteoarthritis and rheumatoid arthritis.

One of ordinary skill in the art would have been motivated to employ the MEK inhibitors of Bridges to treat arthritis such as osteoarthritis and rheumatoid arthritis: the activation of MEK is known to be involved in inflammatory process, such as migration and recruitments of monocytes to the inflammatory sites, in the body. Furthermore, the inhibition of MEK is known to 1) suppress the expression and release of pro-inflammatory cytokines such as interleukin-1β, TNF-α, and interleukin-6; and 2) block and interrupt the adhesion of monocytes to the inflammatory sites. Possessing the teachings of the prior art the skilled artisan would therefore employ any known MEK inhibitors, including those MEK inhibitors of Bridges, to treat arthritis such as rheumatoid arthritis and osteoarthritis, absent evidence to the contrary.

Response to Arguments

Please note that applicants mischaracterize the ground of the rejection under 35 USC 103 set forth in the previous office action mailed June 19, 2002. The claims herein are rejected under 35 USC 103 over Miyazawa et al., Jackson et al., Henry et al., and McGilvray et al. in view of Bridges [emphasis added]. Therefore, there are four primary

references (namely, Miyazawa et al., Jackson et al., Henry et al., and McGilvray et al.) set forth in the instant rejection.

Applicant's rebuttal arguments averring p38 MAP kinase inhibitors are different from the herein claimed MEK inhibitors, which are inhibitors of upstream kinase MEK of raf/MEK/erk casade have been considered, but are not found persuasive. MEK inhibitors, as disclosed in the instant specification page 1, line 5, encompass every types of MAP kinase inhibitors. Therefore, p38 MAP kinase is considered by one of ordinary skill in the art as MEK inhibitors. The broadest claim herein does not distinguish p38 MAP kinase inhibitors from broadly claimed MEK inhibitors as recited herein.

Applicant's rebuttal arguments averring McGilvary alone, in combination with Bridges not providing the motivation to employ MEK inhibitors in the treatment of rheumatoid arthritis have been considered, but are not found persuasive. The rejection is based on the combination of Miyazawa et al., Jackson et al., Henry et al., McGilvray et al., and Bridges. Based on the cited prior art, the inhibition of MEK is known to 1) suppress the expression and release of pro-inflammatory cytokines such as interleukin-1β, TNF-α, and interleukin-6; and 2) block and interrupt the adhesion of monocytes to the inflammatory sites. Therefore, possessing the teachings of the cited prior art, one of ordinary skill in the art would employ any known MEK inhibitors, including those MEK inhibitors of Bridges, to treat arthritis such as rheumatoid arthritis and osteoarthritis, absent evidence to the contrary. No such evidence is seen to be present.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
March 19, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

3/18/03